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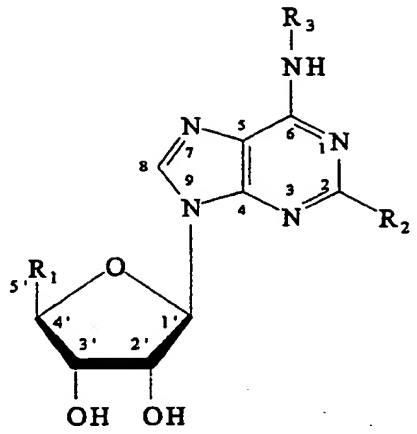
(54) Title: A_3 ADENOSINE RECEPTOR AGONISTS

(57) Abstract

The present invention provides N^6-benzyladenosine-5'-N-uronamide and related substituted compounds, particularly those containing substituents on the benzyl and/or uronamide groups, and modified xanthine ribosides, as well as pharmaceutical compositions containing such compounds. The present invention also provides a method of selectively activating an A_3 adenosine receptor in a mammal, which method comprises acutely or chronically administering to a mammal in need of selective activation of its A_3 adenosine receptor a therapeutically effective amount of a compound which binds with the A_3 receptor so as to stimulate and A_3 receptor-dependent response.

WHAT IS CLAIMED IS:

1. A compound of the formula



wherein R_1 is $R^aR^bNC(=O)$ or HOR^c, wherein R^a and R^b may be the same or different and are selected from the group consisting of hydrogen, C_1-C_{10} alkyl, amino, C_1-C_{10} haloalkyl, C_1-C_{10} aminoalkyl, C_1-C_{10} boc-aminoalkyl, and C_3-C_{10} cycloalkyl, or are joined together to form a heterocyclic ring containing two to five carbon atoms, and R^c is selected from the group consisting of C_1-C_{10} alkyl, amino, C_1-C_{10} haloalkyl, C_1-C_{10} aminoalkyl, C_1-C_{10} boc-aminoalkyl, and C_3-C_{10} cycloalkyl, R_2 is selected from the group consisting of hydrogen, halo, C_1-C_{10} alkylethers, amino, C_1-C_{10} alkylamino, C_2-C_{10} alkenes, C_2-C_{10} alkynes, thio, and C_1-C_{10} alkylthio, and R_3 is selected from the group consisting of R- and S- 1-phenylethyl, an unsubstituted benzyl group, and a phenylethyl or benzyl group substituted in one or more positions with a substituent selected from the group consisting of C_1-C_{10} alkyl, amino, halo, C_1-C_{10} haloalkyl, nitro, hydroxy, acetamido, C_1-C_{10} alkoxy, and sulfo.

2. The compound of claim 1, wherein R_1 is $R^aR^bNC(=O)$, wherein R^a and R^b may be the same or different and are selected from the group consisting of hydrogen,

C_1-C_{10} alkyl, amino, C_1-C_{10} haloalkyl, C_1-C_{10} aminoalkyl, and C_3-C_{10} cycloalkyl, R_2 is selected from the group consisting of hydrogen, halo, C_1-C_{10} alkylethers, amino, C_2-C_{10} alkenes, and C_2-C_{10} alkynes, and R_3 is selected from the group consisting of R- and S- 1-phenylethyl, an unsubstituted benzyl group, and a benzyl group substituted in one or more positions with a substituent selected from the group consisting of C_1-C_{10} alkyl, amino, halo, C_1-C_{10} haloalkyl, nitro, hydroxy, acetamido, C_1-C_{10} alkoxy, and sulfo.

3. The compound of claim 2, wherein R_2 is hydrogen or halo.

4. The compound of claim 2, wherein R^a is hydrogen and R_2 is hydrogen.

5. The compound of claim 4, wherein R_3 is unsubstituted benzyl.

6. The compound of claim 5, wherein R^b is a C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl.

7. The compound of claim 6, wherein R^b is a C_1-C_{10} alkyl.

8. The compound of claim 7, wherein R^b is methyl.

9. The compound of claim 4, wherein R_3 is R-1-phenylethyl, S-1-phenylethyl, or a substituted benzyl.

10. The compound of claim 9, wherein R^b is a C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl.

11. The compound of claim 10, wherein R^b is a C_1-C_{10} alkyl.

12. The compound of claim 11, wherein R^b is methyl or ethyl.

13. The compound of claim 12, wherein R_3 is a substituted benzyl.

14. The compound of claim 13, wherein R_3 is a benzyl substituted in one or more positions with a substituent selected from the group consisting of halo, amino, acetamido, C_1-C_{10} haloalkyl, and sulfo.

15. The compound of claim 14, wherein R_3 is a halo-substituted benzyl.

16. The compound of claim 15, wherein the compound is N^6-3-iodobenzyl-5'-N-methylcarboxamidoadenosine.

17. The compound of claim 2, wherein R^a and R^b may be the same or different and are selected from the group consisting of hydrogen and C_1-C_{10} alkyl.

18. The compound of claim 1, wherein R_1 is $R^aR^bNC(=O)$, wherein R^a and R^b may be the same or different and are selected from the group consisting of hydrogen, C_1-C_{10} alkyl, amino, C_1-C_{10} haloalkyl, C_1-C_{10} aminoalkyl, and C_3-C_{10} cycloalkyl, R_2 is selected from the group consisting of halo, C_1-C_{10} alkylethers, amino, C_1-C_{10} alkylamino, C_2-C_{10} alkenes, C_2-C_{10} alkynes, thio, and C_1-C_{10} alkylthio, and R_3 is selected from the group consisting of R- and S- 1-phenylethyl, an unsubstituted benzyl group, and a benzyl group substituted in one or more positions with a substituent selected from the group consisting of C_1-C_{10} alkyl, amino, halo, C_1-C_{10} haloalkyl, nitro, hydroxy, acetamido, C_1-C_{10} alkoxy, and sulfo.

19. The compound of claim 18, wherein R^a is hydrogen and R_2 is halo, C_1-C_{10} alkylamino, or C_1-C_{10} alkylthio.

20. The compound of claim 19, wherein R_3 is a substituted benzyl.

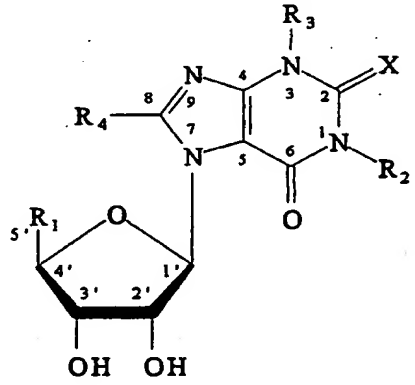
21. The compound of claim 20, wherein R^b is a C_1-C_{10} alkyl.

22. The compound of claim 21, wherein said compound is selected from the group consisting of 2-chloro-N^6-(3-iodobenzyl)-9-[5-(methylamido)-β-D-ribofuranosyl]-adenine, N^6-(3-iodobenzyl)-2-methylamino-9-[5-(methylamido)-β-D-ribofuranosyl]-adenine, and N^6-(3-iodobenzyl)-2-methylthio-9-[5-(methylamido)-β-D-ribofuranosyl]-adenine.

23. The compound of claim 2, wherein R_2 is a C_2-C_{10} alkyne of the formula R'-C≡C- where R' is a C_1-C_8 alkyl.

24. A compound selected from the group consisting of N^6-benzyladenosine-5'-N-alkyluronamide-N^1-oxide and N^6-benzyladenosine-5'-N-dialkyluronamide-N^1-oxide.

25. A compound of the formula



wherein X is O or S, R_1 is $R^aR^bNC(=O)$ or HOR^c, wherein R^a and R^b may be the same or different and are selected from the group consisting of hydrogen, C_1-C_{10} alkyl, amino, C_1-C_{10} haloalkyl, C_1-C_{10} aminoalkyl, and C_3-C_{10} cycloalkyl, or are joined together to form a heterocyclic ring containing two to five carbon atoms, and R^c is selected from the group consisting of C_1-C_{10} alkyl, amino, C_1-C_{10} haloalkyl, C_1-C_{10} aminoalkyl, C_1-C_{10} boc-aminoalkyl, and C_3-C_{10} cycloalkyl, R_2 and R_3 may be the same or different and are selected from the group consisting of C_1-C_{10} alkyl, R- and S- 1-phenylethyl, an unsubstituted benzyl group, and a phenylether or benzyl group substituted in one or more positions with a substituent selected from the group consisting of C_1-C_{10} alkyl, amino, halo, C_1-C_{10} haloalkyl, nitro, hydroxy, acetamido, C_1-C_{10} alkoxy, and sulfo, and R_4 is selected from the group consisting of halo, benzyl, phenyl, C_3-C_{10} cycloalkyl, and C_1-C_{10} alkoxy, with the proviso that if X = O, R_1 is $HOCH_2$, and R_4 = H, then R_2 and R_3 are not C_1-C_4 alkyl.

26. The compound of claim 25, wherein X is O, R_1 is $R^aR^bNC(=O)$, wherein R^a and R^b may be the same or different and are selected from the group consisting of hydrogen, C_1-C_{10} alkyl, amino, C_1-C_{10} haloalkyl, C_1-C_{10} aminoalkyl, and C_3-C_{10} cycloalkyl, R_2 and R_3 may be the same or different and are selected from the group consisting of C_1-C_{10} alkyl, R- and S- 1-phenylethyl, an unsubstituted benzyl group, and a benzyl group substituted in one or more positions with a substituent selected from the group consisting of C_1-C_{10} alkyl, amino, halo, C_1-C_{10} haloalkyl, nitro, hydroxy, acetamido, C_1-C_{10} alkoxy, and sulfo, and R_4 is selected from the group consisting of halo, benzyl, phenyl, and C_3-C_{10} cycloalkyl.

27. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of claim 1.

28. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of claim 2.

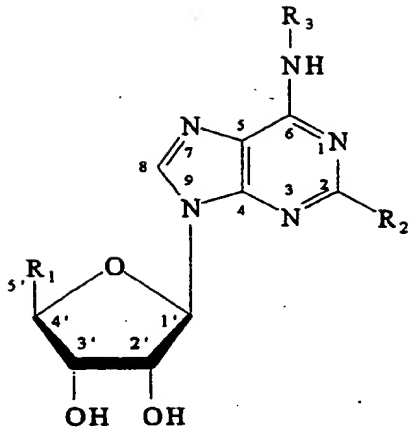
29. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of claim 24.

30. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of claim 25.

31. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of claim 26.

32. A method of selectively activating an A_3 adenosine receptor in a mammal, which method comprises administering to a mammal in need of selective activation of its A_3 adenosine receptor a therapeutically effective amount of a compound which binds with the A_3 receptor so as to stimulate an A_3 receptor-dependent response.

33. The method of claim 32, wherein said compound has the formula



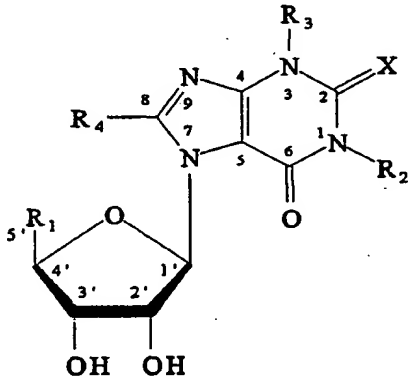
wherein R_1 is $R^aR^bNC(=O)$ or HOR^c, wherein R^a and R^b may be the same or different and are selected from the group consisting of hydrogen, C_1-C_{10} alkyl, amino, C_1-C_{10} haloalkyl, C_1-C_{10} aminoalkyl, C_1-C_{10} boc-aminoalkyl, and C_3-C_{10} cycloalkyl, or are joined together to form a heterocyclic ring containing two to five carbon atoms, and R^c is selected from the group consisting of C_1-C_{10} alkyl, amino, C_1-C_{10} haloalkyl, C_1-C_{10} aminoalkyl, and C_3-C_{10} cycloalkyl, R_2 is selected from the group consisting of hydrogen, halo, C_1-C_{10} alkylethers, amino, C_1-C_{10} alkylamino, C_2-C_{10} alkenes, C_2-C_{10} alkynes, thio, and C_1-C_{10} alkylthio, and R_3 is selected from the group consisting of R- and S- 1-phenylethyl, an unsubstituted benzyl group, and a phenylethyl or benzyl group substituted in one or more positions with a substituent selected from the group consisting of C_1-C_{10} alkyl, amino, halo, C_1-C_{10} haloalkyl, nitro, hydroxy, acetamido, C_1-C_{10} alkoxy, and sulfo.

34. The method of claim 33, wherein R_1 is $R^aR^bNC(=O)$, wherein R^a and R^b may be the same or different and are selected from the group consisting of hydrogen, C_1-C_{10} alkyl, amino, C_1-C_{10} haloalkyl, C_1-C_{10} aminoalkyl, and C_3-C_{10} cycloalkyl, R_2 is selected from the group consisting of hydrogen, halo, C_1-C_{10} alkylethers, amino,

C_2-C_{10} alkenes, and C_2-C_{10} alkynes, and R_3 is selected from the group consisting of R- and S- 1-phenylethyl, an unsubstituted benzyl group, and a benzyl group substituted in one or more positions with a substituent selected from the group consisting of C_1-C_{10} alkyl, amino, halo, C_1-C_{10} haloalkyl, nitro, hydroxy, acetamido, C_1-C_{10} alkoxy, and sulfo.

35. The method of claim 32, wherein the compound is selected from the group consisting of N^6-benzyladenosine-5'-N-alkyluronamide-N^1-oxide and N^6-benzyladenosine-5'-N-dialkyluronamide-N^1-oxide.

36. The method of claim 32, wherein said compound has the formula

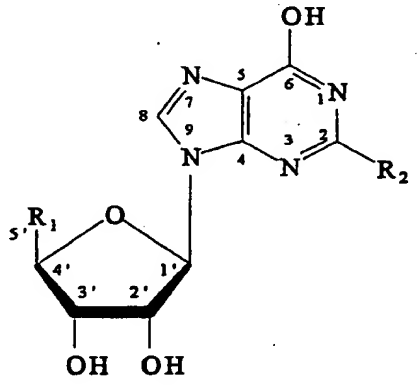


wherein X is O or S, R_1 is $R^aR^bNC(=O)$ or HOR^c, wherein R^a and R^b may be the same or different and are selected from the group consisting of hydrogen, C_1-C_{10} alkyl, amino, C_1-C_{10} haloalkyl, C_1-C_{10} aminoalkyl, C_1-C_{10} boc-aminoalkyl, and C_3-C_{10} cycloalkyl, or are joined together to form a heterocyclic ring containing two to five carbon atoms, and R^c is selected from the group consisting of C_1-C_{10} alkyl, amino, C_1-C_{10} haloalkyl, C_1-C_{10} aminoalkyl, and C_3-C_{10} cycloalkyl, R_2 and R_3 may be the same or different and are selected from the group consisting of C_1-C_{10} alkyl, R- and S- 1-phenylethyl, an unsubstituted benzyl group, and

a phenylether or benzyl group substituted in one or more positions with a substituent selected from the group consisting of C_1-C_{10} alkyl, amino, halo, C_1-C_{10} haloalkyl, nitro, hydroxy, acetamido, C_1-C_{10} alkoxy, and sulfo, and R_4 is selected from the group consisting of halo, benzyl, phenyl, C_3-C_{10} cycloalkyl, and C_1-C_{10} alkoxy.

37. The method of claim 36, wherein X is O, R_1 is $R^aR^bNC(=O)$, wherein R^a and R^b may be the same or different and are selected from the group consisting of hydrogen, C_1-C_{10} alkyl, amino, C_1-C_{10} haloalkyl, C_1-C_{10} aminoalkyl, and C_3-C_{10} cycloalkyl, R_2 and R_3 may be the same or different and are selected from the group consisting of C_1-C_{10} alkyl, R- and S- 1-phenylethyl, an unsubstituted benzyl group, and a benzyl group substituted in one or more positions with a substituent selected from the group consisting of C_1-C_{10} alkyl, amino, halo, C_1-C_{10} haloalkyl, nitro, hydroxy, acetamido, C_1-C_{10} alkoxy, and sulfo, and R_4 is selected from the group consisting of halo, benzyl, phenyl, and C_3-C_{10} cycloalkyl.

38. The method of claim 32, wherein said compound has the formula



wherein R_1 is $R^aR^bNC(=O)$ or HOR^c, wherein R^a and R^b may be the same or different and are selected from the group consisting of hydrogen, C_1-C_{10} alkyl, amino, C_1-C_{10}

haloalkyl, C_1-C_{10} aminoalkyl, C_1-C_{10} boc-aminoalkyl, and C_3-C_{10} cycloalkyl, or are joined together to form a heterocyclic ring containing two to five carbon atoms, and R^c is selected from the group consisting of C_1-C_{10} alkyl, amino, C_1-C_{10} haloalkyl, C_1-C_{10} aminoalkyl, and C_3-C_{10} cycloalkyl, and R_2 is selected from the group consisting of hydrogen, halo, C_1-C_{10} alkylethers, amino, C_1-C_{10} alkylamino, C_2-C_{10} alkenes, C_2-C_{10} alkynes, thio, and C_1-C_{10} alkylthio.

39. The method of claim 38, wherein R_1 is $R^aR^bNC(=O)$, wherein R^a and R^b may be the same or different and are selected from the group consisting of hydrogen, C_1-C_{10} alkyl, amino, C_1-C_{10} haloalkyl, C_1-C_{10} aminoalkyl, C_1-C_{10} boc-aminoalkyl, and C_3-C_{10} cycloalkyl, and R_2 is selected from the group consisting of hydrogen, halo, C_1-C_{10} alkylethers, amino, C_2-C_{10} alkenes, and C_2-C_{10} alkynes.

40. The method of claim 39, wherein R^a is hydrogen and R_2 is hydrogen.

41. The method of claim 40, wherein R^b is a C_1-C_{10} alkyl.

42. The method of claim 41, wherein R^b is methyl or ethyl.

43. The method of claim 40, wherein R^b is a C_3-C_{10} cycloalkyl.

44. The method of claim 43, wherein R^b is cyclopropyl.

45. The method of claim 40, wherein R^b is a C_1-C_{10} aminoalkyl.

46. The method of claim 40, wherein R^b is a C_1-C_{10} aminoethyl.

47. The method of claim 40, wherein R^b is a C_1-C_{10} boc-aminoalkyl.

48. The method of claim 47, wherein R^b is boc-aminoethyl.

49. The method of claim 40, wherein the compound is selected from the group consisting of 5'-N-aminoethylamino-carboxamidoadenosine and 5'-N-boc-aminoethylamino-carboxamidoadenosine.

50. The method of claim 40, wherein R^b is hydrogen.

51. The method of claim 32, wherein said compound is a 1,3-R_1R_2-xanthine-7-riboside, wherein R_1 and R_2 may be the same or different and are selected from the group consisting of hydrogen, C_1-C_{10} alkyl, amino, C_1-C_{10} haloalkyl, C_1-C_{10} aminoalkyl, benzyl, and C_3-C_{10} cycloalkyl, or are joined together to form a heterocyclic ring containing two to five carbon atoms.

52. The method of claim 51, wherein said compound is a 1,3-R_1R_2-xanthine-7-riboside, wherein R_1 and R_2 may be the same or different and are selected from the group consisting of hydrogen, C_1-C_{10} alkyl, amino, C_1-C_{10} haloalkyl, C_1-C_{10} aminoalkyl, benzyl, and C_3-C_{10} cycloalkyl.

53. The method of claim 52, wherein said compound is a 1,3-dialkylxanthine-7-riboside.

54. The method of claim 52, wherein said compound is 1,3-dibutylxanthine-7-riboside.

55. The method of claim 32, wherein said compound is a 5'-R_3-1,3-R_1R_2-xanthine-7-riboside, wherein R_1 and R_2 are selected from the group consisting of hydrogen, C_1-C_{10} alkyl, amino, C_1-C_{10} haloalkyl, C_1-C_{10} aminoalkyl, benzyl, and C_3-C_{10} cycloalkyl, or are joined together to form a heterocyclic ring containing two to five carbon atoms, and R_3 is selected from the group consisting of C_1-C_{10} alkoxycarbonyl and aminocarbonyl, wherein the amino group is unsubstituted or substituted at one or more positions with a C_1-C_{10} alkyl.

56. The method of claim 55, wherein said compound is a 5'-R_3-1,3-R_1R_2-xanthine-7-riboside, wherein R_1 and R_2 are selected from the group consisting of hydrogen, C_1-C_{10} alkyl, amino, C_1-C_{10} haloalkyl, C_1-C_{10} aminoalkyl, benzyl, and C_3-C_{10} cycloalkyl, and R_3 is selected from the group consisting of C_1-C_{10} alkoxycarbonyl and aminocarbonyl, wherein the amino group is unsubstituted or substituted at one or more positions with a C_1-C_{10} alkyl.

57. The method of claim 56, wherein said compound is a 5'-R_3-1,3-dibutylxanthine-7-riboside, wherein R_3 is selected from the group consisting of C_1-C_{10} alkoxycarbonyl and aminocarbonyl, wherein the amino group is unsubstituted or substituted at one or more positions with a C_1-C_{10} alkyl.

58. The method of claim 57, wherein said compound is 5'-methylaminocarbonyl-1,3-dibutylxanthine-7-riboside.

59. The method of claim 51, wherein said compound is chronically administered.

60. The method of claim 55, wherein said compound is chronically administered.

61. The method of claim 58, wherein said compound is chronically administered.

62. The method of claim 32, wherein said mammal has or is at risk of having a condition, disorder, or disease state associated with the cellular release of inositol-1,4,5-triphosphate or diacylglycerol.

63. The method of claim 32, wherein said mammal has or is at risk for hyperactivity and said compound in binding to said A_3 adenosine receptors functions as a locomotor depressant.

64. The method of claim 32, wherein said mammal has or is at risk for hypertension and said compound in binding to said A_3 adenosine receptors functions as a hypotensive agent.

65. The method of claim 32, wherein said mammal has or is at risk for anxiety and said compound in binding to said A_3 adenosine receptors functions as an anxiolytic agent.

66. The method of claim 32, wherein said mammal has or is at risk for cerebral ischemia and said compound in binding to said A_3 adenosine receptors functions as a cerebroprotectant.

67. The method of claim 32, wherein said mammal has or is at risk for seizures and said compound in binding to said A_3 adenosine receptors functions as an antiseizure agent.

68. An assay which comprises providing a compound of claim 1 which has been labeled, contacting a sample with said labeled compound under conditions sufficient to

effect binding between said labeled compound and a component of said sample, and determining whether said binding occurred.

69. An assay which comprises providing a compound of claim 24 which has been labeled, contacting a sample with said labeled compound under conditions sufficient to effect binding between said labeled compound and a component of said sample, and determining whether said binding occurred.

70. An assay which comprises providing a compound of claim 25 which has been labeled, contacting a sample with said labeled compound under conditions sufficient to effect binding between said labeled compound and a component of said sample, and determining whether said binding occurred.

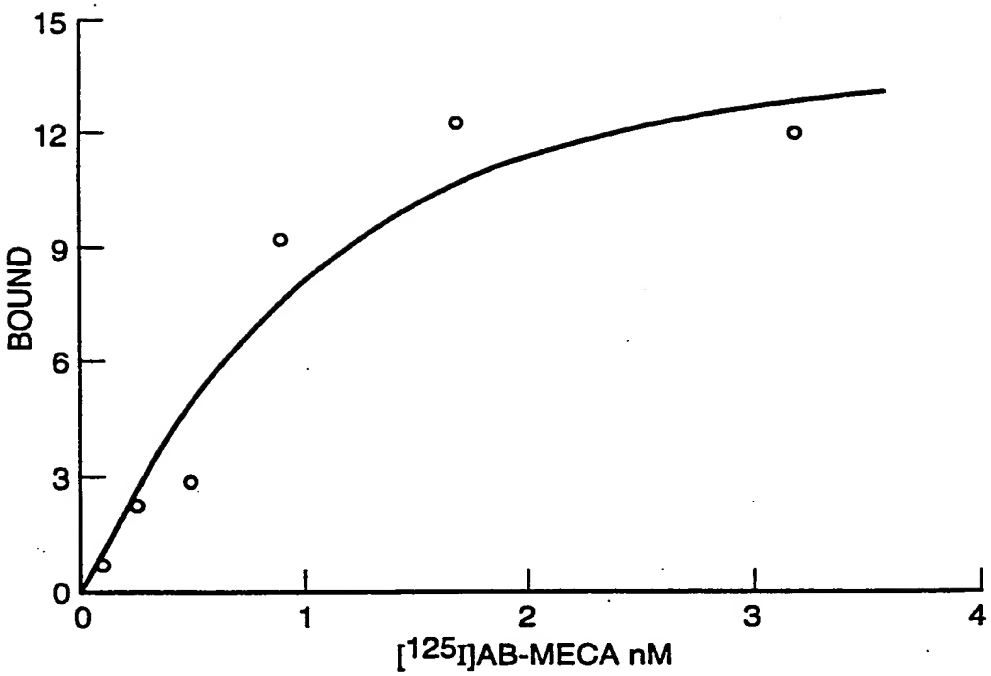
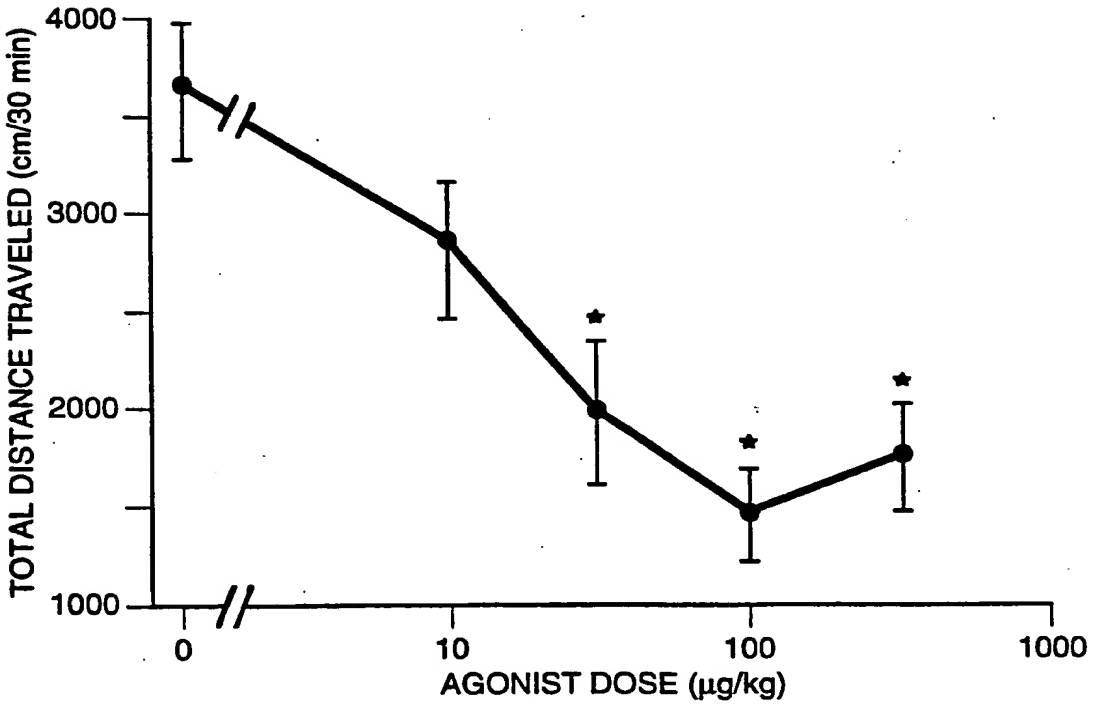

15
12
9
6
3
0
BOUND
0
1
2
3
4
[125I]AB-MECA nM

FIG. 1


4000
3000
2000
1000
TOTAL DISTANCE TRAVELED (cm/30 min)
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10
100
1000
AGONIST DOSE (µg/kg)

FIG. 2

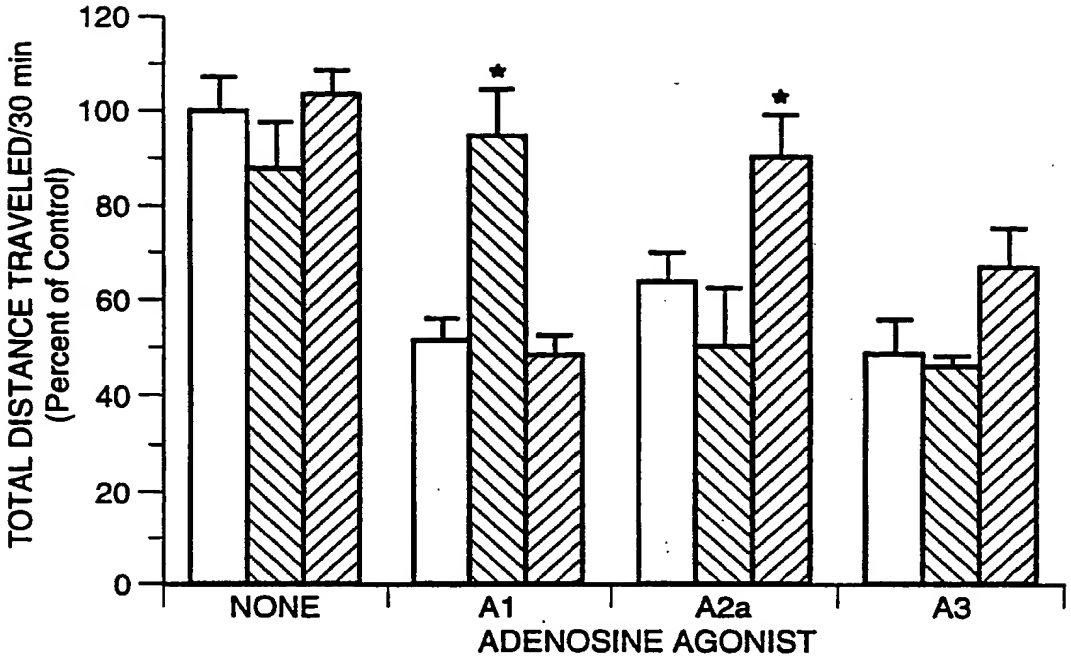
TOTAL DISTANCE TRAVELED/30 min
(Percent of Control)
120
100
80
60
40
20
0
NONE
A1
A2a
A3
ADENOSINE AGONIST

FIG. 3

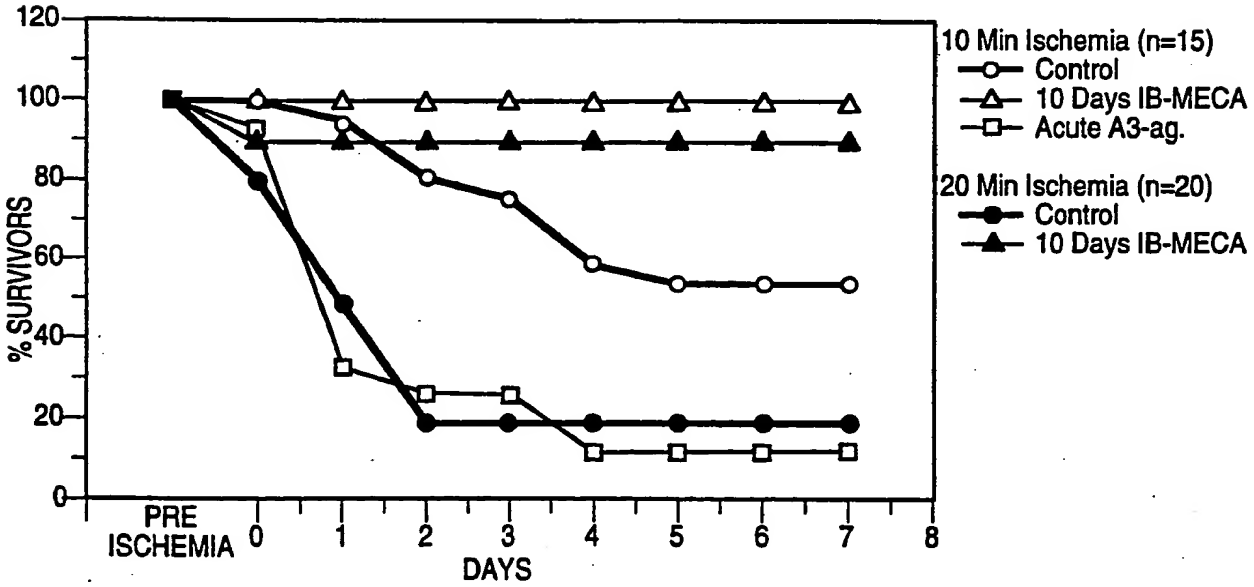
% SURVIVORS
120
100
80
60
40
20
0
PRE ISCHEMIA
0
1
2
3
4
5
6
7
8
DAYS
10 Min Ischemia (n=15)
Control
10 Days IB-MECA
Acute A3-ag.
20 Min Ischemia (n=20)
Control
10 Days IB-MECA

FIG. 4

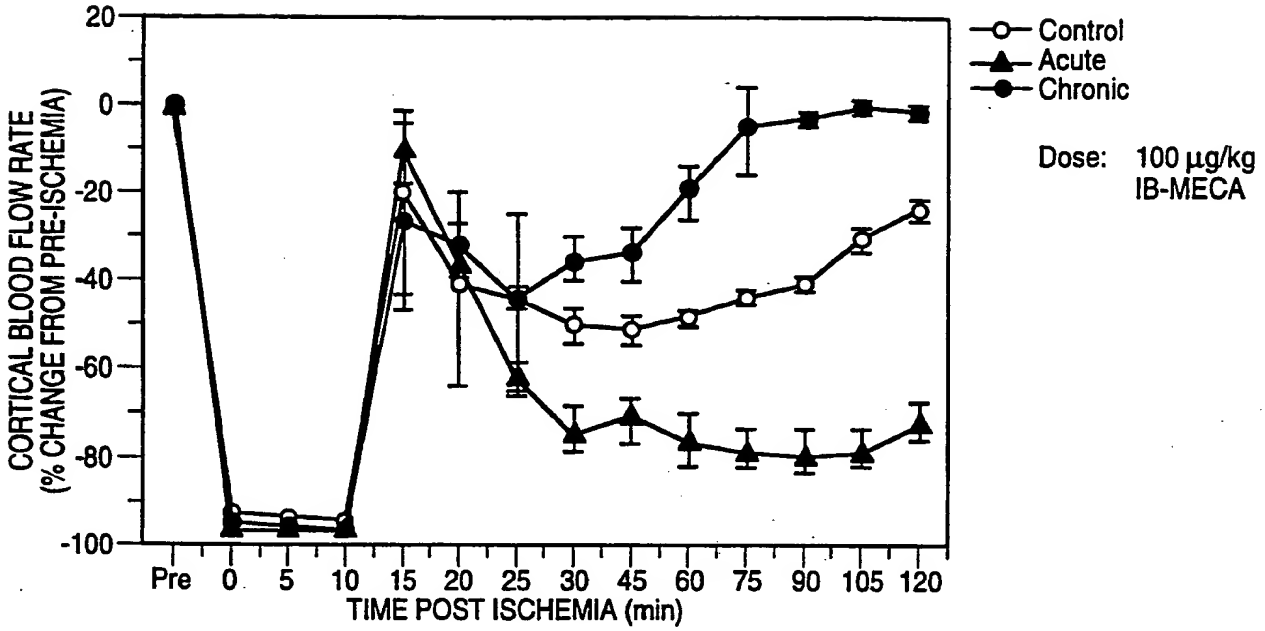
20
0
-20
-40
-60
-80
-100
CORTICAL BLOOD FLOW RATE
(% CHANGE FROM PRE-ISCHEMIA)
Pre 0 5 10 15 20 25 30 45 60 75 90 105 120
TIME POST ISCHEMIA (min)
Control
Acute
Chronic
Dose: 100 µg/kg
IB-MECA

FIG. 5

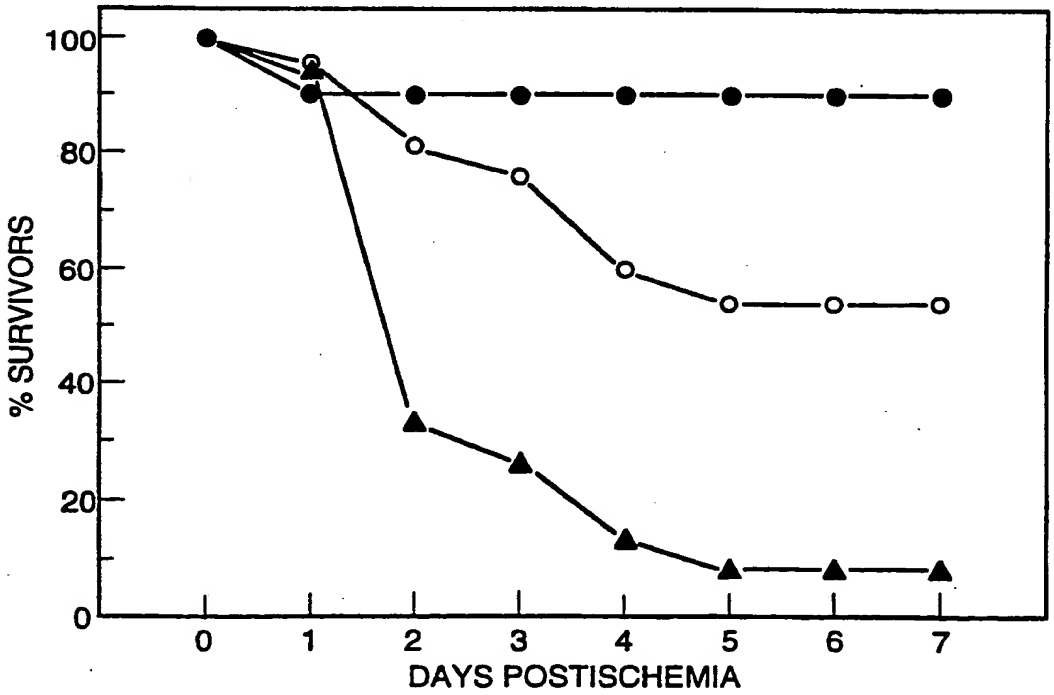
100
80
60
40
20
0
% SURVIVORS
0 1 2 3 4 5 6 7
DAYS POSTISCHEMIA

FIG. 6

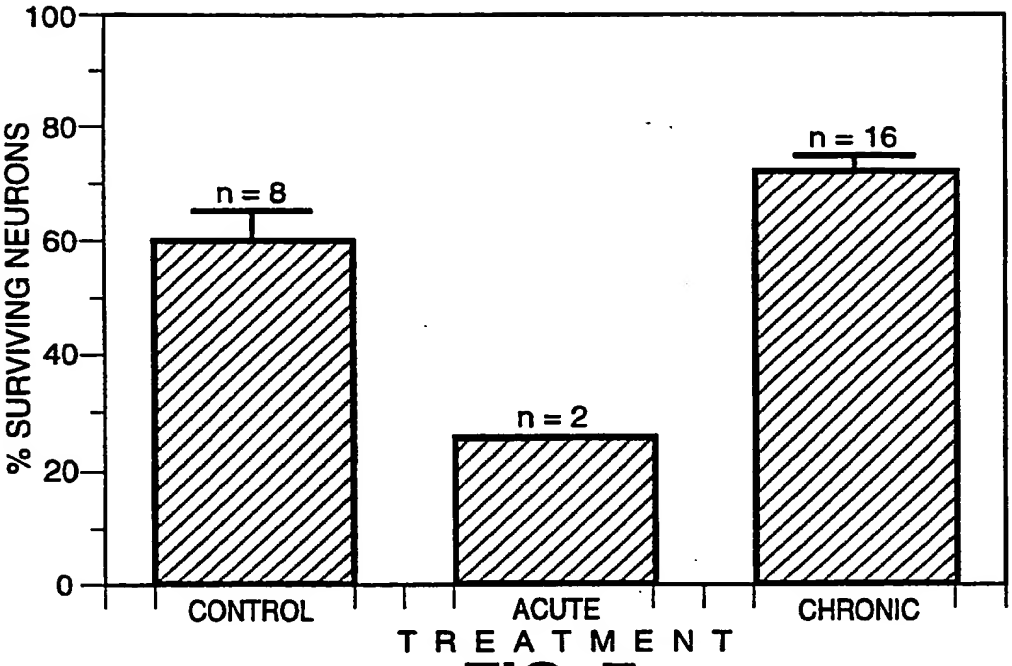
100
80
60
40
20
0
% SURVIVING NEURONS
n = 8
n = 2
n = 16
CONTROL
ACUTE
CHRONIC
TREATMENT

FIG. 7

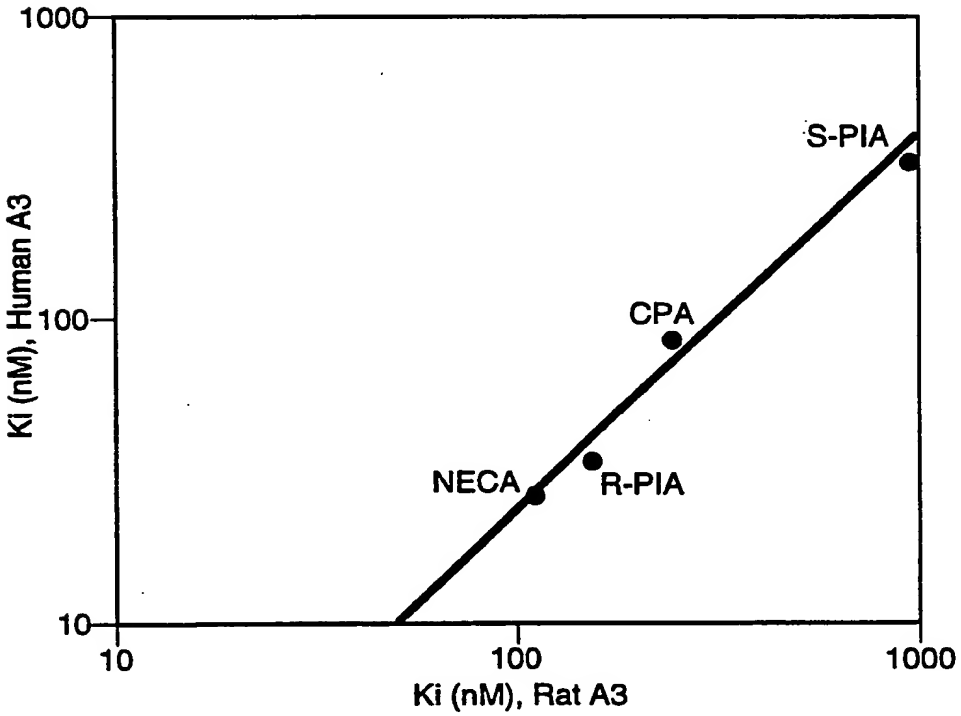
1000
100
10
Ki (nM), Human A3
S-PIA
CPA
NECA
R-PIA
10
100
1000
Ki (nM), Rat A3

FIG. 8

INTERNATIONAL SEARCH REPORT

Inter ...nal Application No
PCT/US 94/07835

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07H19/167 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,86 00310 (NELSON RESEARCH AND DEVELOPMENT COMPANY) 16 January 1986 See the Whole Document, but especially, compounds 23 and 25 on page 11, compound 21 on page 12, compounds 35,36 and 38 on page 15	1-4, 9-15,17
X	DE,A,25 24 284 (BOEHRINGER MANNHEIM GMBH) 28 October 1976 see page 4; examples 1,1a,and,1b	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 October 1994	16. 11. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Scott, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF MEDICINAL CHEMISTRY, vol.35, no.3, 7 February 1992, WASHINGTON US pages 407 - 422 K.A.JACOBSON ET AL. 'Adenosine Receptors: Pharmacology, Structure-Activity Relationships, and Therapeutic Potential.' see examples 12-14	1
A	see the whole document	1-70
X	JOURNAL OF MEDICINAL CHEMISTRY, vol.29, no.6, June 1986, WASHINGTON US pages 989 - 996 S.KUSACHI ET AL. 'Dog Coronary Artery Adenosine Receptor: Structure of teh N6-Aryl Subregion.' See Table 1, compounds 14-31 and 47-63	1
X	CHEMICAL ABSTRACTS, vol. 72, no. 5, 2 February 1970, Columbus, Ohio, US; abstract no. 21921c, K.KOCH ET AL. '2-Aminoadenosine Derivatives with Cardiac Activity.' page 352 ;column 1 ; see abstract & SA,A,6 805 477 (BOEHRINGER, C.F., UND SOEHNE GMBH) 28 January 1969	1
X	CHEMICAL ABSTRACTS, vol. 70, no. 19, 12 May 1969, Columbus, Ohio, US; abstract no. 88212z, W.KAMPE ET AL. 'Adenosines' page 394 ;column 1 ; see abstract & SA,A,6 707 630 (BOEHRINGER C.F., UND SOEHNE GMBH) 21 December 1966	1
X	NUCLEOSIDES AND NUCLEOTIDES, vol.12, no.5, 1993 pages 431 - 439 MOSSHELI A.N. MOSSELHI 'Ribosylation of 8-Substituted Theophylline Derivatives.' See page 432, scheme 1, compound 7	25
P,X	JOURNAL OF MEDICINAL CHEMISTRY, vol.37, no.5, 4 March 1994, WASHINGTON US pages 636 - 646 C.GALLO-RODRIGUEZ ET AL. 'Structure-Activity Relationships of N-6-Benzyladenosine-5'-Uronamides as A3 Selective Adenosine Agonists.' see the whole document	1-17

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International Application No
PCT/US 94/07835

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BRITISH JOURNAL OF PHARMACOLOGY, vol.109, no.1, May 1993 pages 3 - 5 J.R.FOZARD ET AL. 'Adenosine A3 Receptors Mediate Hypotension in the Angiotensin II-supported Circulation of the Pithed Rat.' cited in the application see the whole document	1
A	NUCLEOSIDES AND NUCLEOTIDES, vol.10, no.5, 1991 pages 1191 - 1193 P.J.M.VAN GELEN ET AL. 'Xanthine-7-Ribosides as Adenosine Receptor Antagonists: Further Evidence For Adenosine's Anti Mode of Binding.' cited in the application see the whole document	25

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 94/07835

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 32-67
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 32-67 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 94/07835

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-8600310	16-01-86	US-A-	5310731	10-05-94
		AU-B-	590724	16-11-89
		AU-A-	4497285	24-01-86
		EP-A,B	0191025	20-08-86
		JP-A-	61286398	16-12-86
DE-A-2524284	28-10-76	NONE		
SA-A-6805477		NONE		
SA-A-6707630		NONE		